REMARKS

Claims 39-47 and 49-51 are pending and stand rejected on various grounds in this application. Claims 39-43 have been amended for clarity and to correct inadvertent mistakes pointed out by the Examiner. Applicants submit that no new matter has been added by way of these amendments. Applicants respectfully traverse the rejections.

Claim Rejections – 35 U.S.C. §112 - Enablement

Claims 39-43, 50 and 51 are rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. The Examiner says that "the claims are not enabling because the specification has failed to teach one skilled in the art which changes in the polypeptide to make that will preserve the structure and function....It is known for proteins, that even a single amino acid change or mutation can destroy the function in many instances....The problem of predicting protein structure from sequence data...is extremely complex." The Examiner quotes Wells *et al.* for support. Applicants respectfully traverse this rejection.

As a preliminary matter, Applicants submit that they do not predict protein structure from sequence data in this application and that such a step is not necessary for providing enablement for the variant Claims 39-43, as explained in detail below.

Applicants note that the claimed variants all share the functional recitation that "said polypeptide inhibits VEGF stimulation of endothelial cell growth." Example 66 (page 204) of the present application provides detailed protocols for the VEGF stimulation of endothelial cell growth assay, including the extensive step-by-step guidance in the specification. By following the disclosure in the specification, one skilled in the art can easily test whether a variant PRO224 polypeptide is capable of inhibiting VEGF stimulation of endothelial cell growth. Applicants recognize that there may be polypeptides that (i) are structurally related to PRO224 but which do not inhibit VEGF stimulation of endothelial cell growth or, (ii) do not resemble PRO224 in structure but inhibit VEGF stimulation of endothelial cell growth through mechanisms unrelated to those of PRO224. These structurally related or unrelated polypeptides, however, would

not be encompassed by the instant claims because Applicants claim only those proteins which meet both recitations of the claims, structural and functional. Thus, these recitations clearly act to further define the claimed genus.

The specification further describes methods for the determination of percent identity between two amino acid sequences. (See page 67, line 34, to page 69, line 24). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 112, line 37 to page 115, line 8). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 114). Accordingly, one of skill in the art could identify whether a variant PRO224 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence is identified, the specification sets forth methods for making the amino acid sequences (see page 112, line 37 to page 116, line 35) and methods of preparing the PRO polypeptides (see page 116, line 37 and onward).

More importantly, Applicants note that biological activity in this instance is not claimed based on structural similarity, but instead based on the positive results in the inhibition of VEGF stimulation of endothelial cell growth assay. As discussed above, Applicants claim only those proteins which meet both recitations of the claims, structural and functional. Therefore the effects of mutations on structure-prediction of the variants and the unpredictability in the art are irrelevant to the instant case. Finally, the breadth of the claims are clearly defined by both the structural and functional recitations.

Therefore, Applicants respectfully submit that the specification provides ample guidance such that one of skill in the art could readily test a variant polypeptide to determine whether it inhibits VEGF stimulation of endothelial cell growth by the methods set forth in Example 66.

In conclusion, since the instantly claimed invention is supported by either a credible, specific and substantial asserted utility or a well-established utility, and since the present specification clearly teaches one skilled in the art "how to make and use"

the claimed invention without undue experimentation, Applicants respectfully request reconsideration and reversal of this outstanding rejections under 35 U.S.C. §112, first paragraph, to Claims 39-43, 50 and 51.

Claim Rejections - 35 U.S.C. §112, First Paragraph- Written description

Claims 39-43, 50 and 51 are rejected under 35 U.S.C. §112, first paragraph, for alleged lack of written description. The Examiner says that "the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Applicants respectfully traverse this rejection.

As discussed above, Example 66 (page 204) of the present application provides detailed protocols for the VEGF stimulation of endothelial cell growth assay, including the extensive step-by-step guidance in the specification. Applicants claim only those proteins which meet both recitations of the claims, structural and functional. The specification further describes methods for the determination of percent identity between two amino acid sequences. (See page 67, line 34, to page 69, line 24). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 112, line 37 to page 115, line 8). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 114). Accordingly, one of skill in the art could identify whether a variant PRO224 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence is identified, the specification sets forth methods for making the amino acid sequences (see page 112, line 37 to page 116, line 35) and methods of preparing the PRO polypeptides (see page 116, line 37 and onward).

Therefore, Applicants respectfully submit that the specification provides ample guidance such that one of skill in the art would know that Applicants had possession of

the claimed polypeptides, at the time of filing of the application. Accordingly, Applicants respectfully request reconsideration and reversal of this outstanding rejections under 35 U.S.C. §112, first paragraph, to Claims 39-43, 50 and 51.

Claim Rejections - 35 U.S.C. §112, Second Paragraph

Claims 39-47 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for still reciting part (b) that recited "the polypeptide,.....lacking its associated signal sequence". Claims 39 and 44 are allegedly indefinite for reciting "(a)n isolated polypeptide" and the Examiner indicates that it would be remedial to recite "(t)he isolated polypeptide" instead.

Applicants respectfully submit that Claims 39 and 44 are independent claims and therefore recite "an isolated polypeptide" instead of "the isolated polypeptide". This is consistent with the practice suggested by the Patent Office and therefore, these claims are not indefinite.

Claims 39-47 were indefinite for reciting "the amino acid sequence of the polypeptide shown in Figure 46 (SEQ ID NO:127). Applicants have amended these claims to recite "the amino acid sequence of SEQ ID NO:127."

Claim 39 was indefinite for not reciting "wherein said polypeptide inhibits VEGF stimulation of endothelial cell growth." Claim 39 has been amended accordingly and hence Claims 39-43 are definite.

Claim 44 was rejected as indefinite because it "lacks a biological activity". Applicants submit that this claim is not drawn to variants of SEQ ID NO:127 and instead, is drawn to the amino acid sequence of SEQ ID NO:127; or, the amino acid sequence of SEQ ID NO:127 lacking its associated signal peptide; the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO:127, which inherently, has the biological activity of inhibiting VEGF stimulated endothelial cell growth. Therefore this claim is not indefinite.

Accordingly Applicants submit that this rejection should be withdrawn.

Claim Objection

Claim 49 was objected to for depending from rejected Claim 44. Claim 44 has

been amended and now should be free of rejections. Accordingly, the objection to Claim 49 should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (Attorney Docket No. **39780-1618 P2C13**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: November 1, 2005

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